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RESEARCH ARTICLE

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Myeloperoxidase, superoxide dismutase-3, cardiometabolic risk factors, and distal sensorimotor polyneuropathy: The KORA F4/FF4 study

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Abstract

Background: Oxidative stress has been proposed as important pathomechanism of cardiometabolic diseases and distal sensorimotor polyneuropathy (DSPN). However, the relevance of biomarkers of oxidative stress has not been investigated in this context. Therefore, this study aimed to assess the association of the prooxidant myeloperoxidase (MPO) and the antioxidant extracellular superoxide dismutase (SOD3) with cardiometabolic risk factors and with prevalence and incidence of DSPN.

Methods: Cross-sectional analyses comprised 1069 participants (40.3% with prediabetes and 20.5% with type 2 diabetes) of the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 study (2006-2008), 181 of whom had DSPN at baseline. Prospective analyses included 524 individuals without DSPN at baseline who also participated in the KORA FF4 study (2013-2014), 132 of whom developed DSPN during the 6.5-year follow-up. Serum MPO and SOD3 were measured by ELISA, and their association with cardiometabolic risk factors and DSPN were estimated by using linear and logistic regression analyses.

Results: Higher MPO and SOD levels showed multiple positive associations with cardiometabolic risk factors including age, indices of obesity, insulin resistance, serum lipids, renal dysfunction, and biomarkers of inflammation. Higher MPO levels were associated with prevalent DSPN (fully adjusted OR 1.38 [95% CI 1.10; 1.72] per doubling of MPO). Higher baseline SOD3 levels were related to incident DSPN (age and sex-adjusted OR 2.14 [1.02; 4.48] per doubling of SOD3), which was partially explained by cardiometabolic risk factors.

Conclusions: Systemic levels of both pro- and antioxidant enzymes appear involved in cardiometabolic risk and development of DSPN.

KEYWORDS

cardiovascular risk factors, myeloperoxidase, neuropathy, oxidative stress, polyneuropathy, superoxide dismutase

1 | INTRODUCTION

Oxidative stress has been implicated in the development of type 2 diabetes and its complications.[1-3] One of the most frequent complications of type 2 diabetes is distal sensorimotor polyneuropathy (DSPN),[4,5] which also represents a common comorbidity of cardiovascular diseases (CVDs).[6] Distal sensorimotor polyneuropathy is characterized by a substantial adverse impact on quality of life and a higher risk of mortality,[4,5,7] but our incomplete understanding of its aetiology limits preventive and therapeutic options.

Hyperglycaemia, age, obesity, hypertension, dyslipidaemia, low physical activity, and smoking emerged as risk factors of DSPN, which therefore largely overlap with those identified for type 2 diabetes and CVD.[6,8] These risk factors appear involved not only in the development of DSPN in individuals with prediabetes and type 2 diabetes but also in idiopathic DSPN in elderly individuals with normal glucose tolerance.[9,10] On the other hand, DSPN has been shown to predict CVD in patients with type 2 diabetes.[11] Thus, in order to characterize novel risk factors that specifically influence the risk of DSPN, studies need to take into account cardiometabolic risk factors.

Associations between biomarkers of oxidative stress and DSPN have mainly been assessed in small cross-sectional studies. Increased systemic generation of superoxide anion, higher levels of the protein carbonylation marker methylglyoxal, and lower levels of the antioxidant biomarkers reduced glutathione and glutathione peroxidase in peripheral blood mononuclear cells or serum/plasma have been linked to the presence of DSPN.[12-15] These data point to an imbalance between prooxidant substances and antioxidant capacity in peripheral blood. However, other studies failed to confirm some of these findings.[16] Importantly, higher plasma superoxide generation preceded a larger decline in nerve conduction velocity over 6 years in a prospective study,[17] but we are not aware of further data from large cohort studies in this context.

Although analytical issues such as the instability of many biomarkers of oxidative stress represent major challenges,[2] the measurement of enzymes involved in the generation or dismutation of reactive oxygen species (ROS) allows an estimate of the oxidative stress burden in the circulation. Myeloperoxidase (MPO) catalyses the conversion of H_2O_2 to ROS and is associated with multiple cardiometabolic risk factors and the incidence of cardiovascular events.[18-20] Extracellular superoxide dismutase (SOD3) is the major antioxidant enzyme in the circulation catalyzing the dismutation of superoxide radicals (O_2^-). Lower systemic SOD3 levels were observed in people with type 2 diabetes and DSPN, and gene variants associated with lower SOD3 levels were related to higher cardiovascular risk.[21,22]

We hypothesized that higher serum MPO and lower serum SOD3 are associated with the development of DSPN independently of cardiometabolic risk factors. Therefore, we aimed to assess whether both biomarkers of oxidative stress are associated with prevalent and incident DSPN in a large population-based cohort. We also aimed to characterize the relationship of these 2 proteins with established cardiometabolic risk factors and to investigate to what extent these risk factors might explain any association of MPO and SOD3 with DSPN.

2 | STUDY PARTICIPANTS AND METHODS

2.1 | Study population

The Cooperative Health Research in the Region of Augsburg (KORA) F4 (2006-2008) and FF4 studies (2013-2014) are follow-up examinations of the population-based KORA S4 study (1999-2001), which were conducted in Augsburg (Germany) and 2 surrounding counties. The study design has been described in detail.[23-25] The studies were carried out in accordance with the Declaration of Helsinki, including written informed consent from all participants, and were approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

For the cross-sectional analyses, data from all KORA F4 study participants aged 62 to 81 years (n = 1161) were used. After exclusion of individuals with unclear glucose tolerance status due to missing values for fasting and/or 2-hour glucose, type 1 diabetes, drug-induced diabetes, or other missing covariables (Figure S1), data from 1069 study participants were available for analysis.

For the prospective analyses on incident DSPN, individuals were excluded if no follow-up data from KORA FF4 were available or if they had DSPN in KORA F4, resulting in a sample size of 524 individuals (Figure S1 and Table S1). Follow-up time was 6.46 ± 0.23 years (mean ± SD).

2.2 | Assessment of anthropometric, metabolic, lifestyle, and immunological variables

The standardized assessment of height, body weight, waist circumference, and systolic and diastolic blood pressure has been described before.[23-25] Body mass index (BMI) was calculated as body weight (kg)/(height [m])^2. Actual hypertension was defined as systolic/diastolic blood pressure ≥ 140/90 mm Hg or use of antihypertensive medication given that the study participants were aware of being hypertensive.

The assessment of glucose tolerance status was based on a standard 75-g oral glucose tolerance test for all individuals without known type 2 diabetes using the criteria of the American Diabetes Association for fasting and 2-hour glucose.[26] Known type 2 diabetes was defined if study participants reported a previous diagnosis of type 2 diabetes that could be validated by the responsible physician, or as current use of glucose-lowering medication. Measurement methods of glucose, insulin and HbA_{1c}, and calculation of the homeostasis model assessment of insulin resistance (HOMA-IR) and whole-body insulin sensitivity index (composite) were also reported before.[27-29]

The measurement of serum lipids was done as described,[27,30] the assessment of kidney function from the estimated glomerular filtration rate (eGFR) was based on the chronic kidney disease epidemiology creatinine equation.

Information on medical history, physical activity, smoking, alcohol consumption, and use of medication were obtained by medical interviewers.[24] Individuals were considered physically active if they reported >1 hour of physical activity per week during leisure time in either summer or winter. Smoking status was classified as never, former, or current smoking, and alcohol consumption was classified

as none, moderate, or high based on alcohol intakes of 0, 0.1 to 39.9, or ≥40 g/d for men and 0, 0.1 to 19.9, or ≥20 g/d for women. Neurological conditions that might cause nerve damage were assessed and comprised not only mainly herniated vertebral discs but also complications related to previous stroke or sciatica.

Circulating levels of biomarkers of inflammation were measured as described. Plasma concentrations of high-sensitivity C-reactive protein and interleukin (IL)-18 and serum concentrations of IL-6, tumour-necrosis factor-α (TNFα), IL-1 receptor antagonist (IL-1RA), soluble intercellular adhesion molecule-1, adiponectin, and omentin were quantified by using a high-sensitivity latex-enhanced nephelometric assay (high-sensitivity C-reactive protein) or using ELISAs (all other analytes).[31-33]

2.3 | Assessment of DSPN

The examination part of the Michigan Neuropathy Screening Instrument (MNSI) was used to define presence and incidence of DSPN.[34] The MNSI contains the following items: appearance of feet (normal or deformities, dry skin, callus, infection, fissure, or other irregularities), foot ulceration, ankle reflexes, and vibration perception threshold (VPT) at the great toes. The VPT becomes impaired with increasing age, so that age-dependent limits of normal VPT were used.[35] The neuropathy assessment was extended by the bilateral examination of sensory perception by using a 10-g monofilament (Neuropen),[36] so that the total MNSI score ranged from 0 (all aspects normal) to 10 points.[25] Distal sensorimotor polyneuropathy was defined by using a cut-off at >3 points in accordance with our previous analysis on biomarkers and incident DSPN in this cohort,[25] thus satisfying the minimal diagnostic criteria for possible DSPN.[7]

2.4 | Measurement of MPO and SOD3

Fasting serum samples were stored at −80°C between blood sampling and analysis of MPO and SOD3 concentrations in 2017. Myeloperoxidase concentrations were measured by using the Human Myeloperoxidase Quantikine ELISA (R&D Systems, Wiesbaden, Germany). Extracellular superoxide dismutase concentrations were measured by using the ELISA for SOD3 from Cloud-Clone Corp. (Houston, TX, USA). Limits of detection were 0.16 ng/mL for MPO and 125 pg/mL for SOD3. All sera yielded levels >LOD for both analytes. Coefficients of variation were estimated by using 3 control sera that were measured in duplicates on 16 plates. Mean intra- and inter-assay coefficients of variation were 3.2% and 5.6%, respectively, for MPO and 4.5% and 7.1%, respectively, for SOD3.

2.5 | Statistical analysis

Characteristics of the study population are given stratified by quartiles of serum MPO or SOD3 (with *P* values from linear regression analysis for associations between both $\log_2$-transformed serum levels of both proteins and these characteristics) and stratified by presence of DSPN at baseline (with *P* values from logistic regression analysis, ie, likelihood ratio tests comparing models with the respective variable, age, and sex as independent variables to models with age and sex only).

Cross-sectional associations between $\log_2$(MPO) or $\log_2$(SOD3) and presence of DSPN at baseline (KORA F4) were assessed by multivariable linear regression analysis by using the following potential confounders in line with previous KORA analyses[25]:

Model 1: adjusted for age and sex;

Model 2: model 1 + physical activity, smoking, and alcohol consumption;

Model 3: model 2 + waist circumference and height;

Model 4: model 3 + high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA_{1c}, lipid-lowering medication, hypertension, use of nonsteroidal antiinflammatory drugs, history of myocardial infarction, eGFR, and neurological conditions that might cause nerve damage; and

Model 5: model 4 + IL-6 and TNFα.

Age, alcohol consumption, waist circumference, height, HDL cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA_{1c}, eGFR, IL-6 ($\log_2$-transformed), and TNFα ($\log_2$-transformed) were used as continuous variables in these models.

Prospective associations between $\log_2$(MPO) or $\log_2$(SOD3) and incidence of DSPN between baseline (KORA F4) and follow-up (KORA FF4) were assessed by fitting logistic regression models by using the aforementioned covariables.

Interaction with diabetes status was tested by including diabetes (yes/no) and the interaction terms MPO * diabetes or SOD3 * diabetes in the linear and logistic regression models.

Statistical analyses were carried out with R version 3.3.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and Python version 3.6.1 (Python Software Foundation, https://www.python.org/). Statistical significance was inferred at a 2-tailed *P* value <.05.

3 | RESULTS

3.1 | Associations of MPO and SOD3 with cardiometabolic risk factors

The cross-sectional analysis of the 1069 KORA F4 study participants revealed positive associations of serum MPO and SOD3 with multiple cardiometabolic risk factors after adjustment for age and sex. Higher levels of both proteins were associated with higher age, male sex, higher fasting insulin, insulin resistance, lower eGFR, and higher levels of most biomarkers of inflammation studied (Tables 1 and 2). Among those study participants without antihypertensive medication, both protein levels were inversely associated with diastolic and systolic blood pressure. Both proteins also positively correlated with each other. In addition, higher MPO levels were associated with lower HbA_{1c} and a higher proportion of smokers and ex-smokers (Table 1), whereas higher SOD3 levels were associated with higher BMI and waist circumference, higher 2-hour glucose and 2-hour insulin, higher proportion of impaired glucose regulation and hypertension, lower HDL cholesterol, higher triglycerides, and lower physical activity (Table 2).

TABLE 1 Description of the KORA F4 study population stratified by quartiles of serum concentrations of MPO

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P^a	P^b
n	268	267	267	267		
MPO (ng/mL)	68.7 (53.8; 83.9)	118.7 (105.9; 130.8)	177.0 (159.9; 191.8)	271.3 (233.4; 327.7)		
Age (years)	69.8 ± 5.3	69.9 ± 5.3	70.4 ± 5.5	70.5 ± 5.5	.042	.055
Sex (% male)	48.1	47.9	47.6	61.0	<.001	.007
BMI (kg/m^2)	28.1 ± 3.9	29.0 ± 4.2	29.1 ± 4.7	28.6 ± 4.8	.266	.434
Waist circumference (cm)	96.5 ± 12.1	98.6 ± 12.2	98.7 ± 12.1	99.3 ± 12.2	.106	N/A
Fasting glucose (mmol/L)[c]	5.5 ± 0.7	5.5 ± 0.9	5.4 ± 0.7	5.5 ± 0.6	.088	.029
2-h glucose (mmol/L)[c]	7.2 ± 2.4	7.1 ± 2.5	7.0 ± 2.1	7.1 ± 2.2	.935	.670
HbA_{1c} (%)[c]	5.65 ± 0.39	5.65 ± 0.46	5.60 ± 0.36	5.59 ± 0.37	.022	.011
Fasting insulin (μU/mL)[c,d]	4.6 (3.3; 7.8)	5.3 (3.5; 9.7)	4.8 (3.3; 7.8)	5.2 (3.3; 9.2)	.002	.007
2-h insulin (μU/mL)[c,d]	54.3 (29.9; 93.6)	56.6 (34.5; 88.6)	51.4 (30.2; 83.0)	53.4 (28.3; 89.4)	.315	.597
HOMA-IR[c,d]	1.1 (0.8; 2.0)	1.3 (0.8; 2.5)	1.2 (0.7; 1.9)	1.3 (0.8; 2.4)	.005	.008
ISI (composite) (1/((mmol/L) × (pmol/L)))[c,d]	17.8 (9.8; 29.1)	16.3 (9.2; 26.3)	17.4 (10.4; 28.3)	16.4 (9.6; 28.1)	.335	.540
Glucose tolerance status: NGT/IFG/IGT/ IFG&IGT/ndT2D/kT2D (%)	34.3/23.9/10.8/ 10.4/7.1/13.4	37.8/18.7/10.5/ 12.4/5.6/15.0	44.6/12.4/9.7/ 11.6/6.0/15.7	40.1/22.1/9.0/ 9.7/6.4/12.7	.629	.417
Systolic blood pressure (mm Hg)[e]	121.3 ± 13.6	119.4 ± 14.3	120.1 ± 13.8	117.7 ± 13.2	.023	.022
Diastolic blood pressure (mm Hg)[e]	73.2 ± 8.0	72.4 ± 8.3	71.7 ± 8.1	69.7 ± 8.7	.001	<.001
Hypertension (%)	61.9	59.5	62.9	64.4	.635	.922
Total cholesterol (mmol/L)[f]	5.94 ± 1.05	5.98 ± 1.05	5.89 ± 0.97	5.88 ± 0.96	.930	.888
LDL cholesterol (mmol/L)[f]	3.80 ± 0.91	3.85 ± 0.92	3.74 ± 0.86	3.79 ± 0.90	.959	.998
HDL cholesterol (mmol/L)[f]	1.49 ± 0.40	1.45 ± 0.38	1.47 ± 0.38	1.39 ± 0.33	.161	.464
Triglycerides (mmol/L)[d,f]	1.25 (0.89; 1.75)	1.29 (0.96; 1.82)	1.20 (0.90; 1.69)	1.33 (1.01; 1.82)	.351	.725
Use of lipid-lowering drugs (%)	22.4	24.0	26.2	26.6	.336	.327
eGFR (mL/min per 1.73 m^2)	78.7 ± 13.5	77.3 ± 13.7	75.3 ± 15.7	75.1 ± 16.2	<.001	<.001
Smoking (never/former/current) (%)	57.8/38.1/4.1	50.9/42.7/6.4	54.3/38.6/7.1	40.8/46.4/12.7	<.001	<.001
Physically active (%)	53.0	52.8	46.8	48.7	.064	.108
Alcohol consumption (none/moderate/high) (%)	32.8/54.9/12.3	31.1/49.1/19.9	32.6/52.4/15.0	30.3/49.1/20.6	.151	.201
hs C-reactive protein (mg/L)[d]	1.14 (0.64; 2.24)	1.56 (0.80; 2.72)	1.52 (0.78; 3.26)	2.25 (1.03; 5.51)	<.001	<.001
IL-6 (pg/mL)[d]	1.38 (0.94; 2.12)	1.58 (1.11; 2.17)	1.59 (1.24; 2.43)	2.01 (1.27; 3.13)	<.001	<.001
IL-18 (pg/mL)[d]	296 (247; 378)	312 (253; 412)	332 (255; 423)	330 (252; 440)	.001	.002
TNFα (pg/mL)[d]	1.91 (1.38; 2.86)	2.05 (1.48; 3.01)	1.95 (1.45; 2.74)	2.15 (1.51; 3.11)	.016	.025
IL-1 receptor antagonist (pg/mL)[d]	243 (194; 327)	292 (238; 374)	325 (259; 415)	369 (298; 480)	<.001	<.001
sICAM-1 (ng/mL)[d]	222 (194; 250)	228.0 (198; 256)	227 (198; 262)	242 (213; 274)	<.001	<.001
Adiponectin (μg/mL)	10.03 (6.29; 15.05)	10.28 (6.83; 15.66)	10.31 (6.73; 16.11)	9.76 (6.92; 14.19)	.699	.412
Omentin (ng/mL)	506 ± 156	512 ± 165	508 ± 197	507 ± 163	.422	.350
SOD3 (ng/mL)	126 ± 26	127 ± 23	131 ± 31	135 ± 36	<.001	<.001

Data are given as mean ± SD, median, and 25th and 75th percentiles or percentages, unless indicated otherwise.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hs, high-sensitivity; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; kT2D, known type 2 diabetes; LDL, low-density lipoprotein; MPO, myeloperoxidase; N/A, not applicable; ndT2D, newly diagnosed type 2 diabetes; NGT, normal glucose tolerance; sICAM-1, soluble intercellular adhesion molecule-1; SOD3, extracellular superoxide dismutase; TNF, tumour-necrosis factor.

[a]*P* values are adjusted for age and sex using linear regression analysis. The analysis for age is adjusted for sex only; the analysis for sex is adjusted for age only.

[b]*P* values are additionally adjusted for waist circumference.

[c]Individuals with known type 2 diabetes (n = 152) excluded.

[d]Variables were $\log_2$-transformed for the linear regression analysis.

[e]Individuals with antihypertensive medication (n = 665) excluded.

[f]Individuals with lipid-lowering medication (n = 265) excluded.

Most of the aforementioned associations remained statistically significant after further adjustment for waist circumference. This adjustment slightly attenuated the association between MPO and age (Table 1) as well as the associations between SOD3 and 2-hour glucose, 2-hour insulin, glucose tolerance status, and serum lipids but strengthened the inverse association between MPO and fasting glucose and the positive association between SOD3 and adiponectin (Table 2).

TABLE 2 Description of the KORA F4 study population stratified by quartiles of serum concentrations of SOD3

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P^a	P^b
n	268	267	267	267		
SOD3 (ng/mL)	99 ± 9	119 ± 4	134 ± 5	167 ± 30		
Age (years)	69.7 ± 5.1	70.1 ± 5.5	70.0 ± 5.4	70.8 ± 5.5	.003	.006
Sex (% male)	43.3	50.6	55.8	55.1	.003	.263
BMI (kg/m^2)	28.4 ± 4.4	28.4 ± 4.3	28.6 ± 4.5	29.3 ± 4.5	.003	.132
Waist circumference (cm)	96.5 ± 12.5	97.7 ± 11.7	98.0 ± 11.6	100.8 ± 12.6	<.001	N/A
Fasting glucose (mmol/L)[c]	5.4 ± 0.6	5.5 ± 0.7	5.5 ± 0.6	5.6 ± 0.9	.206	.798
2-h glucose (mmol/L)[c]	6.9 ± 2.0	7.0 ± 2.2	7.0 ± 2.1	7.5 ± 2.8	.038	.210
HbA_{1c} (%)[c]	5.59 ± 0.33	5.65 ± 0.39	5.57 ± 0.33	5.68 ± 0.52	.561	.994
Fasting insulin (μU/mL)[c,d]	4.4 (3.2; 6.9)	5.1 (3.4; 8.1)	4.9 (3.3; 8.7)	5.9 (3.8; 11.2)	<.001	.009
2-h insulin (μU/mL)[c,d]	49.3 (25.4; 75.3)	53.6 (32.1; 94.0)	50.1 (29.2; 89.2)	63.0 (37.3; 98.0)	.015	.238
HOMA-IR[c,d]	1.1 (0.7; 1.7)	1.2 (0.8; 2.1)	1.2 (0.8; 2.2)	1.4 (1.0; 2.8)	<.001	<.001
ISI (composite) (1/((mmol/L) × (pmol/L)))[c,d]	18.8 (11.2; 30.9)	15.5 (10.2; 27.5)	18.2 (9.3; 29.7)	14.2 (8.1; 22.4)	.434	.834
Glucose tolerance status: NGT/IFG/IGT/ IFG&IGT/ndT2D/kT2D (%)	44.4/19.4/10.4/ 10.1/ 4.5/11.2	40.1/20.2/10.5/ 11.6/ 5.6/12.0	39.0/21.0/10.9/ 10.5/ 4.5/14.2	33.3/16.5/8.2/ 12.0/10.5/19.5	.030	.261
Systolic blood pressure (mm Hg)[e]	120.1 ± 12.8	120.5 ± 11.9	119.1 ± 15.2	118.5 ± 15.5	.026	.021
Diastolic blood pressure (mm Hg)[e]	72.5 ± 7.8	72.3 ± 7.7	71.2 ± 8.5	71.1 ± 9.8	.025	.019
Hypertension (%)	53.7	62.5	60.7	71.9	<.001	.004
Total cholesterol (mmol/L)[f]	5.89 ± 1.05	6.03 ± 0.93	5.91 ± 1.08	5.85 ± 0.98	.540	.837
LDL cholesterol (mmol/L)[f]	3.78 ± 0.94	3.85 ± 0.84	3.77 ± 0.95	3.78 ± 0.86	.739	.803
HDL cholesterol (mmol/L)[f]	1.50 ± 0.40	1.48 ± 0.37	1.43 ± 0.36	1.40 ± 0.36	.006	.114
Triglycerides (mmol/L)[d,f]	1.22 (0.84; 1.73)	1.27 (0.96; 1.69)	1.27 (0.95; 1.74)	1.29 (0.97; 1.90)	.035	.276
Use of lipid-lowering drugs (%)	29.1	16.9	25.5	27.7	.534	.503
eGFR (mL/min per 1.73 m^2)	79.3 ± 12.8	78.7 ± 13.0	76.7 ± 14.6	71.6 ± 17.5	<.001	<.001
Smoking (never/former/current) (%)	56.7/39.2/4.1	47.9/42.3/9.7	50.9/42.7/6.4	48.3/41.6/10.1	.139	.121
Physically active (%)	57.8	53.2	49.8	40.5	<.001	.003
Alcohol consumption (none/moderate/high) (%)	33.6/48.5/17.9	32.2/51.3/16.5	27.7/55.8/16.5	33.3/49.8/16.9	.654	.503
hs C-reactive protein (mg/L)[d]	1.34 (0.74; 2.78)	1.34 (0.64; 3.00)	1.52 (0.90; 2.98)	2.04 (1.01; 3.96)	<.001	<.001
IL-6 (pg/mL)[d]	1.52 (1.08; 2.40)	1.48 (0.96; 2.16)	1.53 (1.13; 2.29)	1.84 (1.37; 2.09)	<.001	<.001
IL-18 (pg/mL)[d]	303 (239; 388)	306 (253; 413)	325 (252; 418)	339 (264; 436)	<.001	<.001
TNFα (pg/mL)[d]	1.90 (1.40; 2.69)	1.98 (1.40; 2.87)	1.94 (1.43; 2.79)	2.33 (1.59; 3.48)	<.001	.001
IL-1 receptor antagonist (pg/mL)[d]	286 (222; 378)	295 (230; 376)	320 (246; 413)	344 (258; 461)	<.001	<.001
sICAM-1 (ng/mL)[d]	223 (197; 252)	224 (197; 258)	225 (200; 256)	242 (205; 287)	<.001	<.001
Adiponectin (μg/mL)	10.02 (6.25; 15.34)	10.28 (6.55; 16.36)	10.19 (6.92; 14.09)	9.88 (6.88; 14.62)	.358	.044
Omentin (ng/mL)	500 ± 166	499 ± 181	517 ± 169	517 ± 168	.022	.008
MPO (ng/mL)	137 (90; 195)	138 (86; 193)	148 (102; 220)	166 (100; 230)	<.001	<.001

Data are given as mean ± SD, median, and 25th and 75th percentiles or percentages, unless indicated otherwise. P1 values are adjusted for age and sex using linear regression analysis.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hs, high-sensitivity; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; kT2D, known type 2 diabetes; LDL, low-density lipoprotein; MPO, myeloperoxidase; N/A, not applicable; ndT2D, newly diagnosed type 2 diabetes; NGT, normal glucose tolerance; sICAM-1, soluble intercellular adhesion molecule-1; SOD3, extracellular superoxide dismutase; TNF, tumour-necrosis factor.

[a]*P* values are adjusted for age and sex using linear regression analysis. The analysis for age is adjusted for sex only; the analysis for sex is adjusted for age only.

[b]*P* values are additionally adjusted for waist circumference.

[c]Individuals with known type 2 diabetes (n = 152) excluded.

[d]Variables were $\log_2$-transformed for the linear regression analysis.

[e]Individuals with anti-hypertensive medication (n = 665) excluded.

[f]Individuals with lipid-lowering medication (n = 265) excluded.

3.2 | MPO, SOD3, and prevalence of DSPN

At baseline, individuals with DSPN (n = 181) were older, more frequently male, had a less favourable cardiometabolic risk profile, and higher MPO serum levels than individuals without DSPN (n = 888), whereas SOD3 serum levels did not differ (Table 3). The difference in MPO levels between both groups translated into an age and sex-adjusted OR for prevalent DSPN of 1.36 (95% CI 1.11; 1.67,

TABLE 3 Baseline characteristics of the KORA F4 study population stratified by presence of DSPN

Variable	No DSPN	DSPN	*P*
n	888	181	
Age (years)	69.7 ± 5.3	72.5 ± 5.2	<.001
Sex (% male/female)	49.3/50.7	60.2/39.8	.009
BMI (kg/m^2)	28.4 ± 4.2	30.1 ± 5.2	<.001
Waist circumference (cm)	97.1 ± 11.8	103.7 ± 12.9	<.001
Height (cm)	165 ± 9	168 ± 10	<.001
HbA_{1c} (%)	5.75 ± 0.63	5.96 ± 0.83	.004
Glucose tolerance status (NGT/IFG/IGT/IFG&IGT/ndT2D/kT2D) (%)	40.2/19.9/10.4/10.9/6.5/12.1	34.2/16.0/8.3/11.6/5.0/24.9	.010
Hypertension (%)[a]	61.8	64.1	.355
Total cholesterol (mmol/L)[b]	5.98 ± 1.02	5.63 ± 0.90	.002
LDL cholesterol (mmol/L)[b]	3.84 ± 0.91	3.57 ± 0.81	.005
HDL cholesterol (mmol/L)[b]	1.46 ± 0.38	1.40 ± 0.33	.235
Fasting triglycerides (mmol/L)[b]	1.28 (0.96; 1.76)	1.17 (0.85; 1.81)	.335
Use of lipid-lowering drugs (%)	24.2	27.6	.620
eGFR (mL/min per 1.73 m^2)	77.4 ± 14.5	72.5 ± 16.1	.104
Smoking (never/former/current) (%)	52.1/40.2/7.7	45.3/47.5/7.2	.555
Alcohol intake (none/moderate/high (%)	31.2/52.8/16.0	34.2/44.2/21.6	.008
Physically active (%)	52.0	42.0	.189
Myocardial infarction (%)	5.4	8.8	.650
Neurological conditions that might cause nerve damage (%)	15.8	30.9	<.001
Use of nonsteroidal antiinflammatory drugs (%)[c]	3.6	7.2	.209
MNSI	2.0 (1.0; 2.0)	4.0 (3.5; 4.5)	<.001
MPO (ng/mL)	140 (92; 206)	172 (115; 237)	.002
SOD3 (ng/mL)	126 (111; 142)	129 (114; 150)	.234
hsCRP (mg/L)	1.53 (0.78; 3.20)	1.50 (0.78; 2.84)	.615
IL-6 (pg/mL)	1.55 (1.08; 2.32)	1.85 (1.33; 2.89)	.909
IL-18 (pg/mL)	314 (251; 413)	332 (259; 425)	.399
TNFα (pg/mL)	1.99 (1.45; 2.90)	2.14 (1.56; 3.00)	.864
IL-1RA (pg/mL)	341 ± 180	385 ± 216	.005
sICAM-1 (ng/mL)	235 ± 56	246 ± 63	.102
Adiponectin (μg/mL)	10.11 (6.56; 15.19)	10.18 (6.77; 15.65)	.690
Omentin (ng/mL)	505 ± 170	523 ± 177	.486

Data are given as mean ± SD, median, and 25th/75th percentiles or percentages. The *P* values are derived from logistic regression analysis (likelihood ratio tests comparing models with the respective variable, age, and sex as independent variables to models with age and sex only). All analyses were adjusted for age and sex except associations with age (sex-adjusted only) or sex (age-adjusted only). Biomarkers of oxidative stress and subclinical inflammation were log_2-transformed prior to logistic regression.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL, interleukin; IL-1RA, IL-1 receptor antagonist; kT2D, known type 2 diabetes; LDL, low-density lipoprotein; MNSI, Michigan Neuropathy Screening Instrument; MPO, myeloperoxidase; ndT2D, newly diagnosed type 2 diabetes; NGT, normal glucose tolerance; sICAM-1, soluble intercellular adhesion molecule-1; SOD3, extracellular superoxide dismutase; TNF, tumour-necrosis factor.

[a]Blood pressure of 140/90 mm Hg or higher or antihypertensive medication given that the subjects were aware of being hypertensive.

[b]Individuals using lipid-lowering drugs excluded (n = 265).

[c]Nonsteroidal antiinflammatory drugs except acetylsalicylic acid used as platelet aggregation inhibitor.

P = .003) per doubling of MPO levels (model 1, Figure 1 and Table S2). There was no interaction with diabetes status ($P_{interaction}$ > .05). Further adjustment for multiple cardiometabolic risk factors had almost no impact on this association (fully adjusted model 5: 1.35; 95% CI 1.08; 1.68, *P* = .007). Despite a similar OR, SOD3 levels were not associated with prevalent DSPN in any model due to a considerably wider 95% CI (Figure 1 and Table S2).

3.3 | MPO, SOD3, and incidence of DSPN

Table S1 shows the baseline characteristics of the KORA F4 participants stratified by DSPN incidence. The description of an almost identical study sample has been published before.[25] Briefly, individuals with incident DSPN (n = 132) were older and had an overall less favourable cardiometabolic risk profile including higher

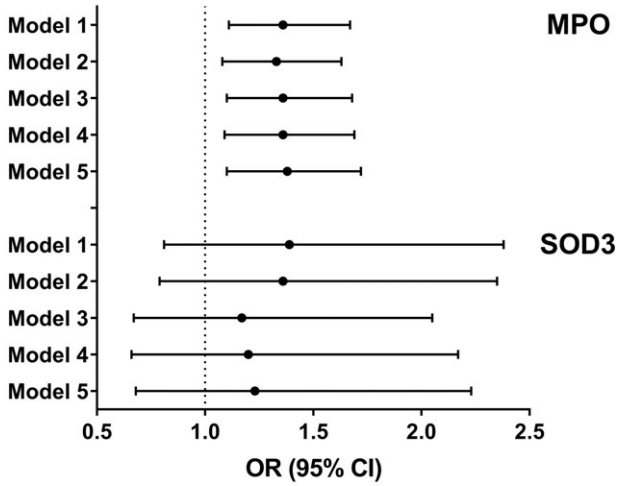

FIGURE 1 Associations of serum concentrations of myeloperoxidase (MPO) and extracellular superoxide dismutase (SOD3) with prevalent distal sensorimotor polyneuropathy. MPO and SOD3 levels were log_2-transformed for the logistic regression analysis, so that OR (95% CI) refers to a doubling in biomarker levels. Model 1: Adjusted for age and sex. Model 2: Model 1 + physical activity, smoking, and alcohol consumption. Model 3: Model 2 + waist circumference and height. Model 4: Model 3 + high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA_{1c}, lipid-lowering medication, hypertension, use of nonsteroidal antiinflammatory drugs, history of myocardial infarction, estimated glomerular filtration rate, and neurological conditions that might cause nerve damage. Model 5: Model 4 + interleukin-6 and tumour-necrosis factor α

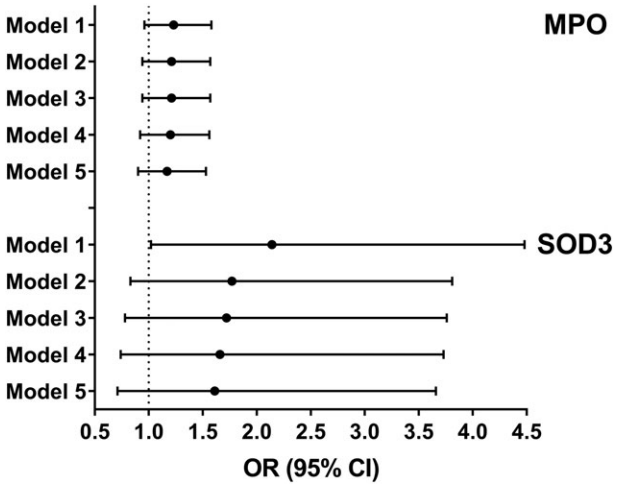

FIGURE 2 Associations of serum concentrations of myeloperoxidase (MPO) and extracellular superoxide dismutase (SOD3) with incident distal sensorimotor polyneuropathy. MPO and SOD3 levels were log_2-transformed for the logistic regression analysis, so that OR (95% CI) refers to a doubling in biomarker levels. Model 1: Adjusted for age and sex. Model 2: Model 1 + physical activity, smoking, and alcohol consumption. Model 3: Model 2 + waist circumference and height. Model 4: Model 3 + high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA_{1c}, lipid-lowering medication, hypertension, use of nonsteroidal antiinflammatory drugs, history of myocardial infarction, estimated glomerular filtration rate, and neurological conditions that might cause nerve damage. Model 5: Model 4 + interleukin-6 and tumour-necrosis factor α

levels of most biomarkers of inflammation than individuals without incident DSPN (n = 392), and adiponectin levels were lower in incident cases (Table S1). Serum MPO levels did not differ between cases and noncases (median [25th and 75th percentiles] 149 [97; 221] versus 132 [88; 198] ng/mL, respectively; age and sex-adjusted P = 0.095), whereas cases had higher SOD3 levels than noncases (129 [97; 221] versus 132 [88; 198] ng/mL; age and sex-adjusted P = .043).

Age and sex-adjusted OR (95% CI) for incident DSPN were 1.23 (0.96; 1.58, P = .098) for MPO and 2.14 (1.02; 4.48, P = .044) for SOD3 (Figure 2 and Table S3). Again, there was no interaction with diabetes status ($P_{interaction}$ > 0.05). However, further adjustment for cardiometabolic risk factors and other confounders in models 2 to 5 attenuated these associations (all P > .1).

4 | DISCUSSION

This study has 3 main findings: (i) Higher levels of serum MPO and SOD3 were associated with multiple cardiometabolic risk factors independent of age, sex, and waist circumference. (ii) Only MPO showed a robust association with prevalent DSPN that was independent of cardiometabolic risk factors, whereas no such association was found for SOD3. (iii) Higher SOD3 levels were associated with higher risk of DSPN, but about half of this association was explained by cardiometabolic risk factors, while no prospective association with incident DSPN was observed for MPO.

4.1 | MPO, cardiometabolic risk factors, and DSPN

Myeloperoxidase, a prooxidant enzyme from leukocytes, is an important source of ROS, which leads to oxidative damage of lipids and proteins. This study represents the most comprehensive population-based analysis of associations between serum MPO and cardiometabolic risk factors so far. Our findings of multiple positive associations with cardiometabolic risk factors including age, HOMA-IR, impaired kidney function, smoking, and subclinical inflammation are in line with the physiological function of MPO and with previous reports linking higher MPO levels with cardiometabolic risk factors and subsequent higher cardiovascular risk in cohorts with preexisting CVD[18,19,37] or in the general population.[20,38] We extend the current literature by showing positive associations between MPO and HOMA-IR, but not with the oral glucose tolerance test-based variables 2-hour insulin and insulin sensitivity index (composite). These data suggest that higher MPO levels are primarily linked with hepatic insulin resistance but less so with peripheral or whole-body insulin resistance. However, we did not find an association with glucose tolerance status. This may be related to the fact that patients with type 2 diabetes showed overall good metabolic control and that the levels of hyperglycaemia in this study population were not pronounced enough to induce notable oxidative stress.

Associations between circulating MPO levels and prevalent or incident DSPN have not been investigated before. We show that higher MPO levels are independently associated with the prevalence of DSPN. With respect to incident DSPN, we observed a positive trend, but adjustment for cardiometabolic risk factors attenuated this

association. The weaker association in the prospective analysis may be attributable to the smaller sample size compared with the cross-sectional analysis. Alternatively, the cross-sectional association may be overestimated because of residual confounding or reverse causality as often seen in cardiovascular research.[39] Thus, MPO may be involved in the pathogenesis of DSPN, but possibly restricted by the available sample size, we cannot provide evidence of its utility as biomarker for incident DSPN in contrast to IL-6 and TNFα, which independently predicted incident DSPN in this study sample.[25]

4.2 | SOD3, cardiometabolic risk factors, and DSPN

Extracellular superoxide dismutase represents the major antioxidant enzyme in the circulation and the most important scavenger of superoxide in the extracellular compartment. It is produced in response to ROS and proinflammatory cytokines such as TNFα and interferon-γ and has neuroprotective effects in vitro.[40] In contrast to MPO which has been investigated before in the context of cardiometabolic risk factors, comparable studies for SOD3 are lacking. Thus, our findings showing associations of higher serum SOD3 levels with higher age, BMI, glycaemia, and insulin resistance (but not glucose tolerance status), hypertension, subclinical inflammation, lower kidney function, and less physical activity are novel and extend the current literature. This study also contains the first observation between higher SOD3 levels and higher risk of developing DSPN, which is partly explained by cardiometabolic risk factors.

Based on 2 previous observations, we had expected associations in the opposite direction. The first study found that SOD3 levels were lower in individuals with recent-onset type 2 diabetes compared with nondiabetic individuals and in diabetes patients with DSPN compared with DSPN-free diabetes patients.[22] The second study reported that gene variants that were linked to higher SOD3 levels had a protective effect on the risk for cardiovascular events in patients with diabetes.[21] Thus, lower antioxidant capacity should be linked to higher cardiometabolic risk.

However, our study provides consistent evidence that both the presence of cardiometabolic risk factors including all aspects of the metabolic syndrome and subclinical inflammation as well as the increased risk of developing DSPN are associated with *higher* SOD3 levels. Overall, these data are comparable to findings for IL-1 receptor antagonist (IL-1RA), a major antiinflammatory regulator.[41] IL-1RA levels are positively associated with multiple cardiometabolic risk factors, and increases in systemic IL-1RA levels are observed 5 to 15 years before the manifestation of type 2 diabetes[42] or cardiovascular events[43] and in people at risk for progression of DSPN.[25] The increases in systemic SOD3 and IL-1RA levels most likely reflect an upregulation due to chronic subclinical inflammation, oxidative stress, and metabolic stimuli. This, however, is not sufficient to protect against the cardiometabolic diseases and DSPN. Interestingly, a similar association of enhanced mitochondrial SOD2 expression with longer diabetes duration and sympathovagal dysbalance has been observed previously.[44]

The discrepancy between the first of the aforementioned studies[22] and our study cannot be explained by technical factors, as both studies used the same assay for quantification of SOD3 and also similar preanalytical procedures. However, the other study[22] was based on a much younger study sample and lacked a population-based design, so that selection bias cannot be excluded.

With respect to the second of the aforementioned studies,[21] it is important to note that a recent meta-analysis showed that genetic upregulation of IL-1RA was associated with lower inflammation and better insulin sensitivity,[45] which mirrors the aforementioned observation of lower cardiovascular risk in individuals with genetically upregulated SOD3 levels.[21] Thus, the results may not be as discrepant as at first sight. Collectively, these findings point toward the necessity to differentiate between genetic and environmental mechanisms to counteract inflammation and oxidative stress.

4.3 | Clinical implications for the prevention and treatment of DSPN

Despite the biological plausibility that oxidative stress is involved in DSPN, prospective studies on biomarkers of oxidative stress and DSPN are very scarce. Our previous study showed an association between higher plasma superoxide production and decline in nerve conduction and cardiac autonomic function over 6 years in patients with diabetes.[17] The present study adds the observation that higher SOD3 levels were associated with incident DSPN in the general population. Thus, studies analysing further biomarkers of oxidative stress are necessary to better understand the role of different prooxidant processes in the development of DSPN. Promising candidates are ROS, further sources of ROS, biomarkers modified by interaction with ROS (eg, biomarkers of lipid peroxidation, tyrosine nitration, and protein carbonylation), and biomarkers produced in response to oxidative stress (eg, other antioxidant enzymes).[2]

The impact of approaches targeting oxidative stress in the prevention and treatment of DSPN has been addressed in few studies. The best evidence for beneficial effects in preventing the progression of DSPN comes from α-lipoic acid,[6,46] but further prevention and intervention trials are necessary to explore this promising avenue of pathogenesis-derived treatment.

4.4 | Strengths and limitations

The strengths of the study include the large sample size, the combination of cross-sectional and prospective analyses, the detailed phenotyping, the population-based design, and the accuracy of the MPO and SOD3 assays, which allowed a valid and comprehensive analysis of the association between circulating levels of both proteins and cardiometabolic risk factors. This study provides the first evidence linking MPO and SOD3 with DSPN based on cross-sectional and prospective associations taking into account multiple cardiovascular risk factors as confounders.

This study also has limitations. First, we were not able to measure ROS or RNS with direct cellular effects because of their short half-life and instability in frozen samples. Thus, further biomarkers need to be investigated in order to assess links among systemic oxidative stress, cardiometabolic risk, and DSPN in more detail. Despite the comparatively large cohort for studies of DSPN, we had a smaller sample size for the prospective compared with the cross-sectional analysis, which

reduced our statistical power. As described,[25] individuals who did not participate in the KORA FF4 follow-up examination had a less favourable cardiometabolic profile including a higher prevalence of type 2 diabetes, which may explain why glucose tolerance status was not associated with incident DSPN in our cohort. Moreover, the study examined older individuals of German descent which limits the generalizability of our findings to younger populations and people with a different ethnic background.

5 | CONCLUSION

Serum levels of MPO and SOD3 showed positive associations with multiple cardiometabolic risk factors. Higher MPO levels were independently associated with prevalent DSPN. We also observed an association between higher SOD3 levels and incident DSPN, but about half of the excess risk was explained by cardiometabolic risk factors. Collectively, our data indicate that oxidative stress and an antioxidative counterregulation may be linked to cardiometabolic risk and the development of DSPN.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

CONTRIBUTION STATEMENT

C.He. and D.Z. designed the study. B.T. contributed to the study design. C.He., C.Hu., M.C.-K., W.R., W.K., A.S., G.J.B., M.H., B.T., A.P., M.R., and C.M. contributed data. C.He. and J.M.K. drafted the statistical analysis plan. J.M.K. performed the statistical analysis. C. He. wrote the manuscript. All authors contributed to, critically revised, and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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